PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CPG/P/222/WOD	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/001264	International filing date *(day/month/year)* 24.03.2004	Priority date *(day/month/year)* 27.03.2003
International Patent Classification (IPC) or national classification and IPC A61K39/02, A61P31/04		
Applicant THE SECRETARY OF STATE FOR DEFENCE		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand 21.10.2004	Date of completion of this report 24.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Teyssier, B Telephone No. +31 70 340-2062

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001264

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-26	as originally filed

Sequence listings part of the description, Pages

1-3	as originally filed

Claims, Numbers

1-18	as originally filed
19-26	received on 25.10.2004 with letter of 21.10.2004

Drawings, Sheets

1-7	as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001264

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 23, 24 (IA)

because:

☒ the said international application, or the said claims Nos. 23, 24 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001264

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25
	No:	Claims	26
Inventive step (IS)	Yes:	Claims	4, 12, 19
	No:	Claims	1-3, 5-11, 13-18, 20-26
Industrial applicability (IA)	Yes:	Claims	1-22, 25, 26
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item I

Basis of the report

The amendments filed with the letter of 21 October 2004 are admissible under Article 19(2) PCT.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 23 and 24 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents, cited in the International Search Report:

D1 Karlsson J *et al.*, *Microbial & Comparative Genomics* 2000, 5(1), 25-39

D2 Ellis J *et al.*, *Clinical Microbiology Reviews* 2002, 15(4), 631-646

D3 Gray C *et al.*, *FEMS Microbiology Letters* 2002, 215(1), 53-56

D3 reports on five strains of *Francisella tularensis* identified within a bank of ten thousand mutants obtained by transposon mutagenesis; the CG57 strain has an inactivated *purF* gene (D1, § bridging p. 54 and 55), therefore the subject-matter of amended claim 26 is not new (Article 33(2) PCT).

D1 discloses the identification of many new genes of *F. tularensis*, with a view to identified target genes that might be mutated to create live vaccine strains (p. 32, first paragraph); the genes of the shikimate and purine pathways are proposed as targets for the construction of rationally attenuated strains (p. 32-35, Table 2). In view of D1, *generic* subject-matter pertaining to *Francisella* strains in which an enzyme of the purine pathway is inactivated and their use as live vaccines does not involve an inventive step under Article 33.3 PCT. This Authority agrees with the submission that D1 merely states the technical problem, outlines in general terms a possible strategy to overcome it and invites to experiment further in the field; considering that no further guidance as to which gene should be mutated is provided, that it is not established whether a clinically effective live vaccine could actually be derived by the strategy

outlined in D1 and considering further that methods still need to be developed to produce mutants in *Francisella* (see D2, p. 639, first § under "Virulence Determinants" and p. 640, last § under "Development of Live Tularemia Vaccines"), the use of inventive skills may well be required in order to put into practice the strategy outlined in D1 and obtain a *specific* attenuated strain of *F. tularensis*.

In the experiments disclosed in the present application, attempts to target the *purA* gene have failed to yield an effective live vaccine strain, however it was shown that the *purF* mutant strain CG57, isolated from a transposon mutagenesis bank and used for comparison (see p. 19), might be used as a live vaccine. Thus the *purF* gene was validated as target for rational attenuation, but not the initially elected target *purA*. In the opinion of this Authority, and in conformity with the principle that the scope of protection shall be commensurate with the contribution to the art, an inventive step under Article 33.3 PCT may be acknowledged only where the technical problem of providing a attenuated live *Francisella* vaccine is actually solved, i.e. only with respect to the targeting of specific genes of the purine pathway, but not for the targeting of the purine pathway as whole, as at least the targeting of *purA* fails to solve the technical problem. Therefore, the subject-matter of claims 4, 12, 19, specifically directed to *purF* mutants, involves an inventive step but the broader subject-matter of claims 1-3, 5-11, 13-18 and 20-25 does not.

An inventive step might be acknowledged for the targeting of further genes of the purine pathway, e.g. *purD*, *purN*, *purT*, *purL* or *purM*, implicitly designated in claims 3, 11 and 18, in view of additional experimental evidence, not to become part of the description, showing that the targeting of these genes also solves the technical problem.

For the assessment of the present claims 1-22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims.

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19. The use according to claim 16, 17 or 18 wherein the gene is *purF*.

20. The use according to claim any of claims 16 to 19 wherein said gene is inactivated by complete or partial deletion mutation or by insertional mutation.

21. The use according to any one of the preceding claims wherein the strain is a strain of *Francisella tularensis*.

22. The use according to claim 21 wherein the strain is a strain of *Francisella tularensis* subspecies *tularenis* or a strain of *Francisella tularensis* subspecies *novicida*.

23. A method of preventing or treating infection by a *Francisella* species, which method comprises administering to an animal an effective amount of a live strain according to any one of claims 1 to 8 or a composition according to any one of claims 9 to 15.

24. A method according to claim 23 for preventing or treating infection by *Francisella tularensis*, wherein the strain of *Francisella* species used in the method is a strain of *Francisella tularensis* subspecies *tularensis* or *Francisella tularensis* subspecies *novicida*.

25. A method for preparing a strain according to any one of claims 1 to 8, which comprises transforming a strain of *Francisella* species so as to inactivate said gene using cryotransformation.

26. A strain of Francisella tularensis subspecies tularensis wherein a gene that encodes a *purF* gene has been inactivated.